First-in-Human Study of CD19/BCMA Dual-Targeting FasT CAR-T GC012F for Patients with Relapsed/Refractory B-Cell Non-Hodgkin's Lymphoma

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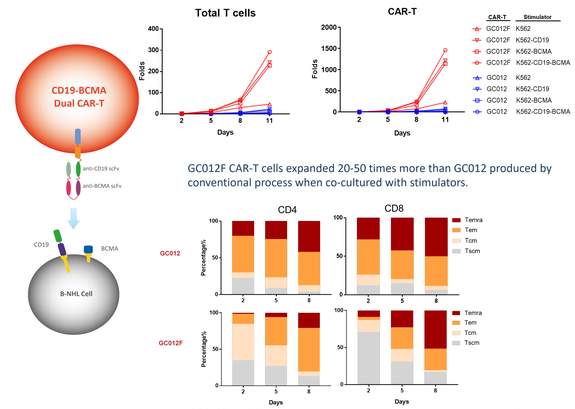
BACKGROUND

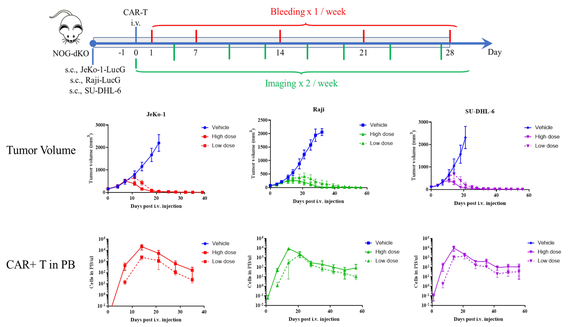
- Relapse due to antigen escape remains a challenge for CD19-directed chimeric antigen receptor T (CAR-T) cell therapy in B cell malignancies including B-cell non-Hodgkin's lymphoma (B-NHL).
- To optimize the depth and duration of response in r/r B-NHL, a dual targeting approach could be beneficial
  - Data suggest that 39% to 97% clinical samples of B-NHL cells express BCMA
- GC012F is a CD19/BCMA dual-targeting CAR-T therapy manufactured on the novel FasT CAR-T platform enabling next-day manufacturing currently in development for multiple myeloma.
- Here, we report the *in vitro* and *in vivo* preclinical data and the preliminary clinical results of the dose escalation study of GC012F in r/r B-NHL (ChiCTR2100047061)

Figure 1. *In Vitro* and *In Vivo* Pharmacologic Activity of GC012F



GC012F CAR-T cells expanded 20-50 times more than GC012 produced by conventional process when co-cultured with stimulators.

GC012F exhibited a younger memory phenotype than the conventionally-manufactured GC012 during proliferation in both CD4 and CD8 populations.



GC012F completely eradicated xenografts in NOG-dKO mice s.c. inoculated with JeKo-1, Raji, or SU-DHL-6 tumor cells.

METHODS

Study Design

Single-center, open label, single-arm investigator-initiated study (N=9-18)

Key inclusion criteria

- Male or Female between 18 to 75 years
- r/r B-NHL with CD19+ and/or BCMA+ expression
- At least one measurable tumor focus: the longest diameter of nodular lesions ≥ 1.5 cm, and the longest diameter of extra-nodal lesions ≥ 1.0 cm (per 2014 Lugano)
- Expected survival ≥ 3 months
- ECOG≤2

Endpoints

- Primary endpoint:
  - Dose limiting toxicities (DLTs) within 28 days
  - Adverse events
- Second endpoints:
  - Objective response rate (ORR, measured by CR+PR) within 90 days
  - Progression free survival (PFS), Overall survival (OS) and duration of remission (DOR)
  - Pharmacokinetics (PK) of GC012F CAR-T cells

Figure 2. Study Design for ChiCTR2100047061

GC012F Dose Escalation	Dose
Dose Level -1	0.5-1 x 10^5 CAR+ T cells/kg
Dose Level 1 (initial dose)	2-3 x 10^5 CAR+ T cells/kg
Dose Level 2	4-6 x 10^5 CAR+ T cells/kg
Dose Level 3	8-12 x 10^5 CAR+ T cells/kg
Lymphodepletion regimens	**Dose**
Fludarabine	25-30mg/m^2/day x 3 days
Cyclophosphamide	250-300mg/m^2/day x 3 days

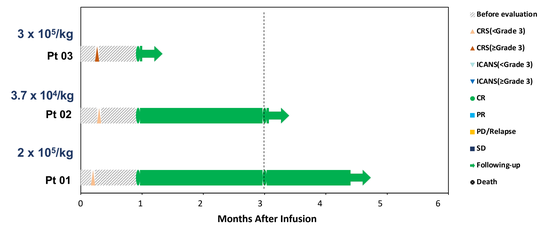
Table 1. Patient Demographics and Disease Characteristics

Characteristic	n = 3
Median age, years (range)	52 (31-60)
Lymphoma subtype, n (%) DLBCL	3 (100)
[1]Disease stage, n (%) IV	3 (100)
ECOG 1, n (%)	3 (100)
Anti-CD20	3 (100)
Immuno-phenotype, n (%) CD19 BCMA	3 (100) 2 (67)
Median prior lines of therapy, n(range)	2 (2-3)
IPI score ≥ 3, n (%)	2 (67)
Relapse/refractory subgroup, n (%) Relapse Refractory	2 (67) 1 (33)
Prior auto-SCT, n(%)	0 (0)

[1]According to Ann Arbor stage.
ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index

RESULTS

Figure 3. Response Assessment - data cut-off February 22nd 2022



- All patients obtained CR at month 1
- Pt 01, Pt 02 maintained CR at month 3

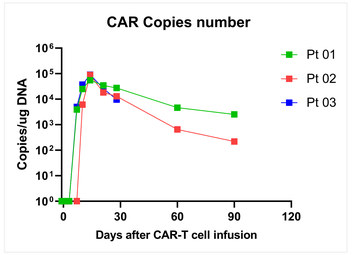
Table 2. Treatment emergent adverse events within 28 days

N=3	All Grades n(%)	Grade ≥3 n(%)
Hematologic TEAEs* within 28 days		
Neutropenia	3 (100)	3 (100)
Leukopenia	3 (100)	2 (67)
Thrombocytopenia	3 (100)	1 (33)
Anemia	2 (67)	2 (67)
Non-Hematologic TEAEs* within 28 days		
LDH increased	1 (33)	0 (0)
Hypoalbuminemia	1 (33)	0 (0)
AST increased	1 (33)	0 (0)
ALT increased	1 (33)	0 (0)

N=3	CRS[&] n(%)	ICANS[&] n(%)
Grade 1	2 (67)	0 (0)
Grade 2	0 (0)	0 (0)
Grade 3	1 (33)	0 (0)
Grade 4/5	0 (0)	0 (0)

*AEs were graded according to CTCAE v5.0, [&]CRS [&] ICANS were graded according to the ASTCT Consensus Grading (Lee et al. 2019)
LDH -Lactase dehydrogenase, AST -Aspartate Aminotransferase, ALT -Alanine Aminotransferase, CRS -Cytokine release syndrome, ICANS -Immune effector cell-associated neurotoxicity Syndrome

Figure 4. GC012F Expansion in Peripheral Blood



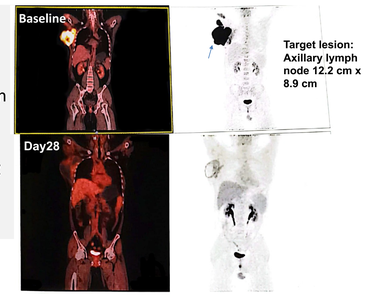
Patient	Dose	Peak CAR Copies/μg DNA
Pt 01	2.0 x 10^5/kg	55222
Pt 02	3.7 x 10^4/kg	89120
Pt 03	3.0 x 10^5/kg	90174

CAR-T expansion was observed in all doses administered

RESULTS

Figure 5. Pt 03 Case Report

- **31-year-old male with R/R DLBCL**
- **2 prior lines of therapy**
  R-CHOP: response unknown
  R-CODOX-M: PD
- **Dose: 3x10^5 CAR+ T cells/kg body weight**
- **CRS Gr 3 , no ICANs**



Assessed CR at day 28

CONCLUSION

- **First-in-human data CD19/BCMA dual CAR-T therapy for r/r B-NHL**
- **In preclinical studies GC012F demonstrated a more robust proliferation and a younger phenotype than conventional CAR-T *in vitro* and effective tumor killing activity in animal models**
- **CAR-T expansion was observed in all treated patients**
- **Early clinical data demonstrate a favorable safety profile to date in three different dose levels**
  - Gr1 CRS:2/2 in doses 3.7x10^4/kg and 2x10^5/kg
  - Gr3 CRS: 1/1 in dose level 3x10^5/kg reverted to grade 2 within 2 days
  - No grade 4/5 - No ICANS in any dose level
- **High response rate**
  - Potent and fast activity with 100% CR rate at 1-month observed in all three pts with r/r B-NHL (DLBCL) including pts with bulky disease
- **The study continues enrolling patients**

ACKNOWLEDGEMENTS

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CONTACT INFORMATION

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